Cytomegalovirus Retinitis in Children - A Guideline for Screening and Treatment

Introduction

Cytomegalovirus (CMV), a member of the Herpesviridae family, is the most common intra-uterine viral infection globally.[1,2] The prevalence of congenital CMV infection in industrialised countries is between 0.5-2% of all live births.[1,2,3] In the developing world, where maternal sero-prevalence rates are much higher, the rate of congenital CMV is between 1-5%.[1] In utero transmission of infection can occur from a primary maternal infection in pregnancy, or recurrent infection. The rate of congenital CMV is higher in primary infections (approximately 40%) than in recurrent maternal infection (0.15-2%).[1,2] CMV is emerging as the leading, non-genetic cause of neurological sequelae in children, since the introduction of the Rubella vaccine.[4] Acquired CMV infection occurs almost exclusively in immune-compromised children.[2] Most commonly it has been reported in HIV positive patients with marked immunosuppression, and in post-transplant patients on immunosuppressive therapy.

A small proportion of children with CMV infection develop sight-threatening ocular disease. In countries with resource limitations, such as South Africa, consensus is lacking regarding the appropriate screening of children for ocular disease, as well as the management thereof. The aim of this guideline therefore is to provide an evidence-based protocol for the screening and treatment of CMV retinitis.

Congenital CMV – the immune-competent child

Approximately 10% of congenital CMV infections are said to be 'symptomatic'.[1,2] These manifest with hepatosplenomegaly (65-75%), petechiae (60-70%), jaundice (50-60%), microcephaly (40-50%), intra-uterine growth restriction (40-50%) and ocular pathology (10-20%).[2,3]

a. 'Symptomatic' infections

There is a paucity of literature on the prevalence and causes of visual loss in congenital CMV. However a review of 146 children revealed that in the 42 patients who were symptomatic for infection, 22% had moderate (20/40-20/200 or poor fixation) to severe

visual impairment (< 20/200 or absent fixation).[5] Ocular involvement took the form of optic atrophy, chorioretinal scars and cortical visual loss.[5] Only one patient had active retinitis at initial screening, with a further 4 showing previous evidence of chorioretinitis.[5] Chorioretinal inflammation occurs in approximately 10-20% of symptomatic patients, the majority of whom have inactive scars at the time of assessment.[2,5,6,7] The burden of disease is thought to be higher in lower socio-economic countries. The retinitis seen in symptomatic, immune-competent patients tends to be a more indolent, granular form of retinitis, which is often self-limiting. A more fulminant form, as seen in immune-compromised adults, has also been described however.[8,9] This can cause visual impairment by involvement of the optic disc or macula.[9]

b. HIV-exposed children

HIV-exposed children, born to mothers with CMV co-infection, have a higher rate of congenital CMV (4.5%) when compared to HIV-unexposed infants (2%).[2] They often present with severe symptomatic disease and have been shown to have a higher mortality rate.[10] A Cape Town-based study found the congenital CMV birth prevalence in 748 HIV-exposed infants to be 2.9%. A maternal CD4 count of <200 cells/μL was independently associated with congenital CMV.[11] The authors recommended a high index of suspicion for congenital CMV, in 'asymptomatic' babies with 2 or more of the following risk factors: HIV-exposed infants with maternal CD4 < 200 cells/μl; early (within 4-6 weeks) HIV PCR positive; unexplained underweight for gestational age (UWGA) and/or thrombocytopaenia.[25]

c. Asymptomatic Infections

The prevalence of visual Impairment is extremely low in asymptomatic patients and studies suggest asymptomatic patients need not undergo fundal screening.[5,6]

<u>Acquired CMV - the immune-compromised child</u>

a. HIV

CMV can be acquired by vertical transmission, as well as horizontal transmission through contact with essentially all bodily fluids.[2] There are age-related sero-prevalence rates for CMV infection and these vary widely, depending on social customs and living conditions.[1,2] In Africa and Asia there are high general sero-prevalence rates and the majority of people are infected with CMV by early adolescence.[2,10]

The rate of CMV retinitis in HIV-infected infants is lower than that found in adults.[2,12,13] In adults, prior to the advent of highly active anti-retroviral therapy (HAART), the rate of CMV retinitis was between 20% and 40%, compared to children, at approximately 5%.[2] However CMV retinitis accounts for 25% of CMV-related AIDS defining illness in children.[2] The mechanism by which retinitis occurs at lower CD4 levels in children is unclear. Infants have a more immature immune system and are more likely to suffer from a primary

infection, rather than reactivation of latent infection.[12] Retinitis is said to be less common in primary infection. CMV retinitis in children with HIV, has a higher predilection for the posterior pole and tends to be bilateral (89-100%), whereas the incidence of bilateral disease in adults is approximately 33%.[9,12]

In a study of opportunistic infections associated with paediatric HIV infection prior to HAART, the rate of CMV retinitis was estimated to be 0.5/100 child years.[2,14] This varied according to CD4 count, with a rate of 1.1/100 child years in CD4<15%, and 0.1/100 child years in CD4<25%.[2,14] The overall rate has dropped to <0.5/100 child years post-HAART.[2,14] The incidence of CMV retinitis among HIV positive children is reported to be between 1.85-33%. (Table 1)[12,13,15-17]

Table 1.Incidence of CMV retinitis in HIV positive children

Study	CMV Retinitis	Country
Kestelyn et al [13] (n=162)	1.85%	Rwanda
Chadwani et al [16] (n=131)	2.3%	USA (New York)
Dennehy[15] (n=87)	2.3%	USA (Atlanta)
Du et al [12] (n=116)	3.4%	USA (Houston)
Biswas et al [17] (n=15)	33%	India

CMV retinitis in young, HIV-infected children is frequently asymptomatic and only discovered on routine clinical examination.[2] Older children might complain of floaters or flashes.[2,12] The retinitis may be in the form of an indolent, granular type, or maybe fulminant, as seen in adult CMV infection.[2,9] There are currently no clear guidelines on when to screen HIV positive children for retinitis. Extrapolated cut-off values using CD4 counts have been trialed, based on findings in adult patients.[12] A prospective review of 173 patients found an incidence of 4 out of 116 (3.4%).[12] All four developed retinitis once their CD4 count had fallen to less than 20cells/μL, or CD4 to absolute lymphocyte (ALC) ratio less than 2%.[12] Dennehy et al reported on similar CD4 levels, with the 2 cases in their series of 87 having a CD4 of less than 10cells/μL.[15]

b. Transplant recipients

CMV infection can be transmitted in both solid organ and haematopoetic stem cell transplantation.[18,19,20] CMV infection is one of the most common complications following solid organ transplantation and results in significant morbidity and graft loss.[19] The highest risk of CMV retinitis is in solid organ transplants, where the donor is positive and the recipient negative.[18] In stem cell transplant, the highest risk is in donor negative, recipient positive cases.[20] High risk patients should be monitored closely with serial quantitative PCR, and should also receive prophylactic anti-viral treatment with acyclovir or valacyclovir.[19,20] CMV retinitis in transplant patients is commonly bilateral and tends to require prolonged treatment, until immune-suppressive therapy can be tapered and the patients' T-cells can form immunity.[18] Quantitative nucleic acid amplification testing

(QNAT) is the preferred method of detecting disease and response to treatment.[19,20] Transplant recipients with suspected CMV disease and positive QNAT should have fundal screening for retinitis.[18,19,20] Patients with retinitis or solid organ disease should be treated with gancyclovir or valgancyclovir, depending on the severity of disease.[19] If there is severe disease with concerns over oral absorption, intravenous gancyclovir should be used.[19] Initial therapy is twice daily gancyclovir or valgancyclovir for at least two weeks, until viral eradication is achieved on two assays.[19]

Testing for CMV

The gold standard for the diagnosis of congenital CMV infection is the isolation of virus in cultures from urine, saliva or blood.[2,7,21] Infection does not necessarily equate to disease, but culture of virus from buffy-coat blood increases the likelihood that disease or symptoms are as a result of CMV infection.[2,7] Cultures can take up to three weeks to yield results however. Centrifugation-assisted shell vial culture amplification techniques can detect CMV within 16-40 hours of culture inoculation.[2,7] CMV PCR on urine specimens has a sensitivity and specificity that approaches 100% and may be useful in cases where more urgent management decisions are needed.[2] Quantitative viral load can also be obtained and is useful in monitoring response to treatment. Saliva PCR testing is as reliable as urine sampling, with the added benefit of being easy to obtain.[22] It is important that urine or saliva specimens be taken within the first 3 weeks after birth, as positive results after 3 weeks do not differentiate congenital from acquired infection.[2,7,21]

In acquired infection, the virus may be shed in urine and nasal secretions for several years post-infection. The peak shedding prevalence in children is at 1-2 years of age, and this is the key transmission factor for pregnant women.[23] In a review of the clinical utility of CMVuria for ophthalmic care in HIV positive adults, Ghellrich et al identified that patients with CD4 counts <50cells/μL, with CMV urine culture positive, had a seven-fold risk for the development of retinitis.[24] Whilst isolation of the virus in any age group indicates infection and not necessarily disease, plasma PCR may be more useful in identifying immunocompromised children at risk of development of disease.

Several antibody/antigen-based tests have also been described.[2] Due to transplacental transfer of antibody, positive serum antibody testing may reflect previous maternal CMV infection and not necessarily infection of the infant.[2] Other methods involve the detection of viral antigen or DNA, and include the urine DEAFF (detection of early antigen fluorescent foci) test, CMV specific IgM, pp65 antigenaemia and CMV DNAemia in peripheral blood leucocytes.[2]

Based on current evidence, urine or saliva PCR testing in newborns within the first 2-3 weeks of life, is a reliable, non-invasive first line investigation to confirm congenital CMV infection.[7,22] This would be the investigation of choice in South Africa. In older children with HIV, urine PCR or culture is adequate to identify those at risk for the development of retinitis, when used in conjunction with the CD4 count.[24]

Treatment

The best evidence for the treatment of congenital CMV is supplied by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (CASG).[25] This study was designed to establish the safe dose of intravenous (IV) gancyclovir. The CASG followed on with a phase III randomised control trial, to determine the effect of gancyclovir treatment on hearing loss in symptomatic patients.[7,25] It established that a significantly higher proportion of infants who received therapy went on to have normal hearing at 6 months of age, compared to untreated patients.[7,25,26] There were also improvements in secondary markers, such as increased growth parameters during therapy, resolution of abnormal liver function profiles, clearance of CMV from urine cultures and fewer neurological sequelae at 1 year follow-up.[25,26] A safe dosage regimen was found to be 6mg/kg of intravenous gancyclovir twice daily for 6 weeks.[2,25] The major side effect was neutropaenia, which occurred in 63% of patients.[2,25] Of these, 48% required a dose adjustment, but the majority were able to complete the treatment course.[25] Gancyclovir has also been given intravitreally in children with CMV retinitis.[2,7] This treatment modality has limitations however, mainly the requirement of general anaesthesia for each injection.[2,7]

More recent studies have been conducted on the use of valgancyclovir (the oral pro-drug of gancyclovir), which has been approved for use in the treatment of adult CMV infection.[26] In neonates, there is emerging pharmacokinetic data which recommends a dose of 15-16mg/kg twice daily, and is equivalent to the IV bioavailable gancyclovir dose.[7,27] Neutropaenia appears to be less common with use of valgancylcovir (38% vs 63%).[7] Other antiviral agents such as foscarnet and cidofovir have also been described in the treatment of CMV infection in adults, but have not been used in children.[2,7] IV gancyclovir and valgancyclovir remain the agents of choice for the treatment of CMV infection in children. In South Africa, the current recommendation is the use of IV gancyclovir for 2 weeks, followed by valgancyclovir for 4 weeks.[28]

Table 2. Drug information for gancylclovir & valgancyclovir

Drug	**Dosage**	**Duration of Therapy**	**Side Effects**	**Monitoring**
Gancyclovir	6mg/kg twice daily intravenously	6 weeks[25] Alternatively 2 weeks, followed by valgancyclovir for 4 weeks[28]	Neutropaenia, thrombocytopaenia *Cessation of therapy if absolute neutrophil count <500 cells/µL, or platelet count <25 000 cells/µL	Weekly full blood count, liver function tests, creatinine, urea and electrolytes

Valgancyclovir	16mg/kg twice daily orally	6 weeks	Neutropaenia, thrombocytopaenia *Cessation of therapy if absolute neutrophil count <500 cells/µL or platelet count <25 000 cells/µL	Weekly for the first two weeks, then every two weeks full blood count, liver function tests, creatinine, urea and electrolytes

Rationale for the screening and treatment of CMV retinitis in children

a. Congenital Infection

The effectivity and treatment duration for congenital CMV retinitis in children is not well established. Several isolated case reports describe treatment regimens of between 2 and 6 weeks, with mixed results. One described anti-viral treatment for congenital CMV retinitis for 6 months, due to recurrence of chorioretinitis after initial cessation of IV gancyclovir therapy.[29] Whitely's series of 14 children treated for chorioretinitis reported resolution in 8 out of 14 children on treatment with IV gancyclovir, while Kimberlin's review of 8 cases reported no difference in time to resolution of chorioretinitis.[30,31] The rationale for screening symptomatic patients however, is that it helps confirm the diagnosis of congenital CMV and may provide further motivation for the initiation of treatment. Treatment, in turn, reduces sensorineural hearing loss and improves secondary markers and may cause resolution of the chorioretinitis in some cases.

b. Acquired Infection

In older, immune-compromised children, resolution of the chorioretinitis has been demonstrated with treatment and it is recommended that this be continued until immune reconstitution has been achieved (CD4 >100 cells/uL).[2] In these children, valgancyclovir is the treatment modality of choice.[2]

Ocular screening protocol

Screening involves examination of the fundus using indirect ophthalmoscopy, through a dilated pupil. Symptomatic congenital CMV patients are often systemically unwell and a thorough peripheral retinal examination can be challenging. Arrangements with the paediatric intensive care clinician should be made, so that a safe ocular examination can be performed.

When and how to screen

A summary of the recommended screening protocol is set out in Appendix 1.

Conclusion

Congenital CMV infection is the most common intra-uterine infection. Only 10% of congenital CMV infections are symptomatic for disease and whilst the estimated prevalence of chorioretinitis among symptomatic patients is between 10-20%, it is virtually absent in asymptomatic infections. Due to the high maternal sero-prevalence rates of CMV in developing countries such as South Africa, an appropriate screening protocol for CMV retinitis would be useful in guiding clinical management. Symptomatic patients with proven congenital CMV infection (CMV urine positive) should be screened. The role of gancyclovir in the prevention of sensorineural hearing loss is well-established. Screening for retinitis can help confirm the diagnosis and provide motivation for the initiation of treatment. Apart from reducing sensorineural hearing loss, treatment results in improvement in secondary markers, such as increased growth parameters, resolution of abnormal liver functions and fewer neurological sequelae.

CMV retinitis in HIV-infected children is more commonly bilateral and prompt treatment may preserve visual function. HIV positive children with marked immune-suppression (CD4 <20cells/μL or <2%) should have regular screening for retinitis, until immune reconstitution is established. Treatment with intravenous gancyclovir, or alternatively oral valgancyclovir should be initiated, in conjunction with the infectious disease clinician overseeing the treatment of HIV.

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